

Review

Cellular Senescence, a Novel Area of Investigation for Metastatic Diseases

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Abstract: Metastasis is a systemic condition and the major challenge among cancer types, as it can lead to multiorgan vulnerability. Recently, attention has been drawn to cellular senescence, a complex stress response condition, as a factor implicated in metastatic dissemination and outgrowth. Here, we examine the current knowledge of the features required for cells to invade and colonize secondary organs and how senescent cells can contribute to this process. First, we describe the role of senescence in placentation, itself an invasive process which has been linked to higher rates of invasive cancers. Second, we describe how senescent cells can contribute to metastatic dissemination and colonization. Third, we discuss several metabolic adaptations by which senescent cells could promote cancer survival along the metastatic journey. In conclusion, we posit that targeting cellular senescence may have a potential therapeutic efficacy to limit metastasis formation.

Keywords: cellular senescence; metastasis; metabolic adaptation; invasion



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1. Introduction

The word “metastasis” is derived from the Greek words meta (meaning beyond) and stasis (indicating the basic concept of motion from one site to another). Indeed, metastasis development requires that cancer cells leave the primary cancer site and disseminate in the bloodstream until seeding to a permissive secondary site. From extensive research, we now know that metastasis underlies the capacity for physical movement, but also the epigenetic, transcriptional and secretory plasticity needed to survive [1]. Metastasis is the most lethal consequence of cancers, but only a few cancer cells survive the initial dissemination. This apparent vulnerability is counterbalanced by the proliferation of a tiny proportion of disseminated cancer cells (DCCs), which are difficult to target for therapeutic purposes [2].

Metastasis does not necessarily follow a linear model of progression. Some cancer cells most likely were ‘born to be bad’, wherein invasive and even metastatic potential is specified early, instead of acquiring deleterious genetic modification through a series of clonal expansions [3]. Regardless of cancer origin, DCCs need to finely tune the balance between cell proliferation and resting status, which is commonly known as “dormancy”, to evolve into a lethal form of metastasis. These features are theoretically intrinsic properties of cancer cells, but even in the first studies of Steven Paget’s seed and soil hypothesis, it was evident that the crosstalk with the microenvironment was of high importance for the success of distant organ colonization. Several studies report that cancer cells need to continuously adapt to changing environments during dissemination, including their metabolism to survive and seed new tumors, at the expense of other abilities [4].

Cellular senescence is a complex stress response. Stimuli of induction and common phenotypes are shown in Figure 1 and are extensively reviewed elsewhere [5]. The main features of senescent cells are a consequence of a dynamic remodeling in morphology, chromatin and cellular metabolism, which confer their typical flat large shape, loss of proliferation potential and inhibition of cellular apoptosis. Cellular senescence is also linked to cancer. As a stable cell cycle arrest, senescence is, in the short-term, tumor-suppressive. Indeed, the loss of proteins required for senescence, such as p53, p16^{INK4a} or Rb, is a common step in carcinogenesis in human tumors and animal models [6–8]. Senescence accumulates at high levels in pre-malignant lesions and at lower levels in invasive diseases [9–11], supporting its role as barrier in malignant progression. However, the percentage of senescent cells in a tumor may vary according to the cancer type and chemotherapy treatments, which also cause aging in cancer cells [12]. Senescent cells also drive inflammation through the secretion of a mélange of factors collectively referred to as the senescence-associated secretory phenotype (SASP), by which they can also manipulate tissue microenvironments; therefore, the activation of their secretome and the resulting beneficial or detrimental effects are context-dependent [8]. Nonetheless, targeting senescent cells has emerged as a new therapeutic approach to treat age-related diseases, and this treatment approach has also been extended for cancer. Indeed, cancer cells' one-time senescence is more vulnerable to "senolytic" drugs, which target the anti-apoptotic response active in senescent cells. In this context, the removal of senescent cancer cells after chemotherapy treatment may represent a viable option to maximize the conventional therapy and prevent cancer relapse. In addition, there is an increased attention regarding the role of cellular senescence in metastasis. The pioneering work of Young Hwa Kim indicates that senescent cancer cells are actively involved in the invasion and metastasis of thyroid cancer [13]. More recently, Sugimoto's group demonstrated that even in melanoma, senescent cells promote metastasis in a non-cell-autonomous manner [14]. Far from being an exception, these studies revealed a tight connection between cellular senescence and DCs, which helps in understanding the role of senescent cells in mechanisms beyond metastasis progression and opens unprecedented opportunities for the development of ad hoc senolytics as novel therapeutic tools for metastatic diseases.

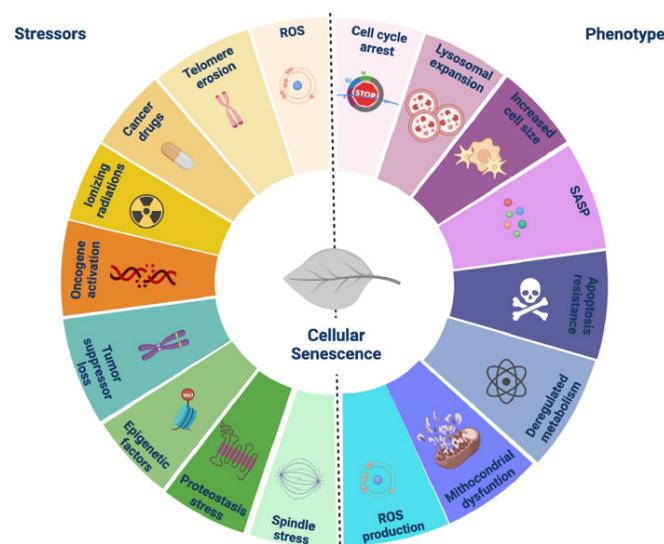


Figure 1. Senescence-inducing stimuli and related phenotypes.

In this review, we discuss the growing evidence for the dynamic interplay between cellular senescence and the process of metastasis. We focus on features of senescent cells that are shared with metastatic cells and are known to promote metastasis progression. We also explore the cancer-metabolic traits required for cancer cells to survive and soil in

secondary organs and their connection with cellular senescence. These traits may then be explored as targets for a new generation of therapeutic approaches.

2. Invasion: Lessons from Mammalian Placenta

The degradation of the tumor basement membrane is the first step in cancer cell invasion. DCs gain access to the vasculature initially, and then escape by extravasation and home toward a target organ following a chemokine gradient. The evidence to support the migratory properties of senescent cells comes from their recent detection in lymph nodes and lymphovascular channels in human thyroid cancer [13]. Since a considerable number of primary human cancers accumulate senescent cells at marginal zones, it is also most likely to expect senescent cell dissemination in other cancer types [13,15]. However, this feature still needs to be validated experimentally and the underlying molecular mechanism must be further explored.

Valuable clues to the role of senescent cells in cell metastasis can be inferred from placentation during embryonic development [16]. The placenta is a provisional fetal organ, which develops from the blastocyst after implantation, and it is involved in the physiological adaptation of the mother to immunological acceptance, nourishment and support of the developing embryo. As the placenta develops, it invades surrounding organs, behaving in some ways like cancer [17]. The placenta generates from trophoblast, the outer layer surrounding blastocyst, which drives the attachment to the uterine epithelium and then differentiates by fusion in the syncytiotrophoblast. This structure is a multinucleated layer which does not show any proliferative activity but displays an invasive phenotype [18,19]. Indeed, the syncytiotrophoblast exhibits the characteristic of cellular senescence, including SA- β -gal activity and p16, p53 and SASP factors with invasive properties [20]. Because the syncytiotrophoblast invasion of maternal tissues is critical for placentation, failure of these cells to undergo cell senescence and elicit the SASP, including the expression of extracellular matrix-degrading enzymes such as MMP2 and MMP9, compromises mouse placental development, causing intrauterine growth restriction during pregnancy [21]. However, in the presence of a cohesin defect, the natural program of placental senescence is exacerbated by persistent DNA damage, resulting in a negative impact on embryo outcome, partly restored by the inhibition of cytokine signaling [22].

Similar secreted cytokines with analogous functions have been described in cancer. Indeed, the IL-6 and IL-8 signaling pathways have shown to have both cell-autonomous and paracrine effects on stromal surroundings, playing a role in angiogenesis, epithelial to mesenchymal transition (EMT) and immune-suppressive responses in several cancers [23,24]. CCL5 is elevated in tumor-conditioned lymphatic endothelial cells and directs the dissemination of tumor cells into lungs and lymph nodes, promoting angiogenesis and colonization in distant organs [25]. CXCL1 is critical for premetastatic niche formation in the liver [26]. Therefore, it is not surprising that senescent cells similarly manipulate the microenvironment to promote the invasion of nearby tissues, such as the placenta. Indeed, in melanoma, soluble E-cadherin produced by senescent cells promoted ECM remodeling, increasing *in vitro* and *in vivo* the invasion properties of cancer cells. The elimination of senescent cells suppressed lung metastasis, indicating that the inhibition of senescence or related SASP can alter the metastatic potential in melanoma [14]. Considering the active involvement of proinflammatory cytokines in metastatic niche formation, it is possible that also for other types of cancers, senescent cancer cells could survive during dissemination and exploit their secretory phenotype to promote non-senescent cancer cell invasion in distant organs. In support of this hypothesis, we report below the characteristics needed for metastasis outgrowth (Figure 2).

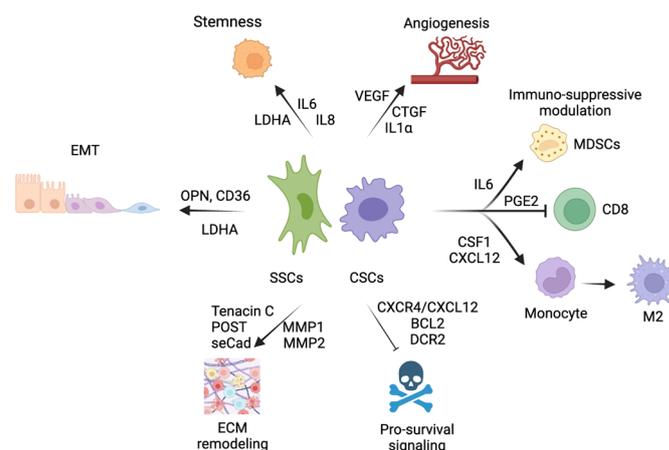


Figure 2. Summary of the factors secreted by senescent cancer cells and stromal senescent cells in each feature required for cell invasion. SSCs (senescent stromal cells); CSCs (cancer senescent cells); seCad (soluble E-cadherin).

3. Common Features Required for Cell Invasion and Colonization

3.1. Fusogenic Potential

Cell fusion is a physiological process in placentas and mammalian livers [27], bone [28] and muscles [29], where it contributes to the acquisition of a mature tissue phenotype. In cancer, cell fusion could combine properties of distinct cells to confer a functional advantage. Indeed, multiple experiments have shown that tumor cells become more aggressive after spontaneous fusion with cells of target organs, such as bone marrow cells, or acquire invading properties, perhaps by fusion with stroma or macrophages [30–32]. Hybrid cells have been shown to express several genes associated with tumor invasion and metastasis, such as SPARC, MCR1 and MET [32].

How cell fusion and cellular senescence are related in cancer remains unclear, although there is a common consensus that the fusion of normal and cancer cells can lead to cell cycle arrest [33,34]. The mutation of the tumor suppressor and senescence-effector p53 confer novel proliferating skills to hybrids, supporting a link between cell fusion and cellular senescence. For example, the overexpression of ERVWE1, the placental endogenous fusogen, and the measles virus (MV) in normal human fibroblasts and human alveolar adenocarcinoma cells (A549) results in the formation of syncytia with senescence features [20]. Many viruses evolve proteins that can prevent infected cells from undergoing senescence [35], suggesting that cellular senescence is a natural consequence of viral infection. Alternatively, senescence could prevent optimal viral replication, and therefore could be an important defense against viral infections. Indeed, the resulting polynucleated fused cells exhibit a senescence phenotype and the activation of p53- and p16–pRb main molecular effectors but also increased tumorigenicity assessed by colony assays. This dual activity may be explained by the pleiotropic function of the SASP.

ERVWE1 is expressed in cancer cells of multiple origins and mediates the fusion of cells in human tumors, including breast and colon cancer [36–38]. Even if every cell fusion event does not result in the induction of cellular senescence [39], it is likely that cellular senescence is a frequent outcome in tumoral hybrids. Indeed, the fusogenic potential of many tumors has been estimated at around 1%. [36,38–40]. Considering that the diameter of cancer cells spans from 15 to 25 μm , a metastatic tumor with a volume of 1 cm^3 could contain at least one million of senescent hybrids. Notably, despite the oncogenic potential of cell fusion, most cases of cell fusion do not lead to cell transformation [33], suggesting that interaction with the tissue microenvironment is still a limiting or a promoting factor.

3.2. Polyploidy

Polyploidy is an important consequence of cell fusion, but can also occur by other processes such as endoduplication. Polyploidy is included in the developmental programs

of many organs, including placenta, liver, heart and bone marrow [41–44]. Interestingly, in all cited areas, the acquisition of an extra amount of DNA coincides with growth restrictions, even though a direct connection between senescence features and ploidy increase is not yet conclusively demonstrated for each. In cancer, polyploidy is often a consequence of exposure to DNA damage or mitotic-checkpoint-targeting drugs [45]. The resulting polyploid tumor cells, referred to as Polyploid Giant Cancer Cells (PGCCs), have a large size, multiple nuclei, active metabolism and markers typical of therapy-induced senescence (TIS), including cell cycle arrest and secretion of tumor-promoting factors [46]. Not all PGCCs are β -gal positive, as described for MCF7 breast carcinoma cells after irradiation [47]. The authors explained this paradox by tracing simultaneous positivity for stemness and linked the absence of β -gal staining to an involvement in self-renewal [48]. Alternatively, Mirzayans et al. described active p53 as a determinant for the development of senescence in cancer cells rather than low β -gal activity in PGCCs. This result was shown in several human cell lines after ionizing radiation or chemotherapeutics [49].

PGCCs have been extensively identified in multiple cancers, including colon, melanoma, lung, pancreas, breast, ovarian, prostate, renal, thyroid and urinary bladder—and clinically detected in lymph nodes of metastatic prostate cancer [50]. Whole-Genome Doubling (WGD) was identified in 37% of solid tumors [51] and proposed as a marker of poor prognosis [52], suggesting that polyploidy in cancer cells can have a detrimental effect. Conversely, a protective role of polyploidy was identified in diethylnitrosamine (DEN) and high-fat diet models of liver carcinoma [53], so the effects of polyploidy are at least somewhat context-dependent.

3.3. EMT–MET Stemness

The transdifferentiation from an epithelial to mesenchymal state (EMT) and the inverse process, known as mesenchymal–epithelial transition (MET), are dynamically involved in cancer cell adaptation and survival [54]. The impact of full EMT or MET profiles on metastasis has been the center of an important debate in recent years, largely due to experimental limits in the ability to detect and follow EMT in clinical settings or with appropriate preclinical models [55]. EMT programs differ based on the inducing pathways, driver genes and cell populations [56]. Nevertheless, studies demonstrate that EMT is crucial for metastasis initiation and chemoresistance [57,58], transforming epithelial cells into invading cells, which disseminate and adapt to stress [59]. In contrast, tumors return to their epithelial state by MET during colonization [1,60,61], which appears to be crucially controlled by niche signals [62].

In aging, several reports describe the involvement of cellular senescence in promoting stemness and EMT features in an intrinsic manner. As stated above, senescent PGCCs often display EMT stem-like properties [63–65]. Those features are observed independently of polyploid status. Indeed, the overexpression of oncogenic H-RasG12V in normal mesothelioma cells or after pemetrexed treatment resulted in senescence induction and EMT with chemoresistance properties [66]. In acute lymphoblastic and myeloid leukemia, we described a new mechanism called senescent associated stemness (SAS), in which after DNA damage these cells developed senescence-associated stemness features, promoted by the activation of a Wnt embryonic development pathway [67]. When p53-dependent cell cycle arrest was blocked, these cells displayed higher tumor-initiating capacity than their senescent counterparts after transplantation in immune-competent recipient mice. Furthermore, the coexistence of the senescence marker p16Ink4a with markers of stemness and metastatic potential has been identified in patients of non-responsive breast cancer tumors after neoadjuvant chemotherapy [68]. These findings underly the intrinsic pro-tumoral nature of senescent cancer cells, which also develop EMT and stemness traits in humans [69,70]. Of note, this result is often achieved after chemotherapy, suggesting a secondary “dark side” to this type of clinical intervention.

In addition, stromal senescent cells can promote EMT and stemness through the SASP in pre-malignant or normal cells. Senescent fibroblasts or their conditioned medium stimu-

late premalignant epithelial cells to proliferate in culture and form tumors in mice [71]. In pre-malignant mammary or prostate epithelial models, cells become invasive and undergo malignant transformation [72]. These effects were largely due to interleukin IL-6 and IL-8 [62], and were later validated in rectal cancer and mesothelioma [66,70].

Osteopontin (OPN) was identified as one of the most highly elevated transcripts in senescent fibroblasts [69,73,74]. OPN promotes preneoplastic human keratinocyte cell growth both in vitro and in vivo [75]. Blocking OPN in breast cancer cells decreases the expression of SNAIL, SLUG and TWIST, indicating that OPN is critical for EMT and tumor metastasis even in a cell-autonomous manner. Additionally, OPN nuclear translocation induces MET and metastatic colonization in HCCLM3 human hepatocellular carcinoma cell lines after subcutaneous injection in athymic mice [76]. OPN translocation is driven by the SASP factor vascular endothelial growth factor (VEGF) from the microenvironment. The detection of nuclear OPN in clinical specimens of lung metastases supports the existence of this mechanism in human cancers [75]. Therefore, multiple SASP factors could interact synergistically to support tumor metastasis from different cellular sites along the metastatic journey.

Cancer-associated fibroblasts (CAFs) are known to have metastasis-promoting functions [77]. Intriguingly, CAFs frequently exhibit SASP-like factors and are enriched in senescent fibroblasts. CAFs have been shown to produce ECM niche components such as periostin (POSTN) and tenascin C [78,79], which are produced by senescent fibroblasts [80]. In addition, TGF- β released from colorectal cancer cells stimulates CAFs to secrete IL-11, which feeds back to tumor cells to activate STAT3 signaling, favoring the survival of metastatic cells in the liver [81]. IL11-induced secretome in primary cultures of human kidney, lung or skin fibroblasts comprises several SASP factors, including IL6, IL8 and CCL20, which are also important in the tumor microenvironment [82]. Even though the numbers of senescent CAF have not been identified in all contexts, experimental studies suggest that targeting senescent fibroblasts in this context has substantial consequences for disease relapse. Indeed, cancer therapy promotes the generation of senescent fibroblasts, which contribute to therapy resistance and increase cancer spread and relapse [83].

Senescent cancer cells can also induce metastatic activity in non-senescent surrounding cancer cells. Her2-dependent senescent MCF7 cells, when co-injected orthotopically with MDA-MB-231 epithelial cells in nude mice, promoted non-senescent cancer cell growth and invasion by their secretome [84]. Paracrine senescence can also involve endothelial cells and immune cells (see below). Together, these reports indicated that EMT and stemness are intrinsic properties of senescent cells that can also be induced in the surrounding microenvironment to promote the invasion of DCS and to set up a more permissive niche by SASPs.

3.4. Angiogenic and ECM Remodeling Properties

A key function of the pre-metastatic niche is to facilitate the landing of cancer cells, providing anchorage while circumventing anoikis and apoptosis [85]. Disseminating cancer cells benefit from angiogenesis and vascular leakiness, which can also have proinflammatory effects increasing the levels of chemoattractant factors, also increasing the recruitment of circulating tumor cells. The ECM is also important in metastatic seeding, as it provides enrichment in fibronectin, TGF- β , MMPs and other remodeling factors essential for permissive composition and stiffness [86–88]. All of these features are modulated by the SASP in primary tumors and by intrinsic resistance of senescent cells to apoptosis [89]. MMPs and factors related to matrix extracellular remodeling are active component of SASPs [90]. Following ionizing radiation, the co-culture of fibroblasts increased breast cancer cell invasiveness through the release of MMPs from senescent fibroblasts [91]. MMP-1 and MMP-2 secreted from senescent skin fibroblast also promote tumorigenic keratinocyte invasion by activating serine/threonine protein kinase PAR-1 [92]. The SASP also contains many pro-angiogenic factors (VEGF, GRO, CTGF, FN, laminin, PA, MMPs, PGE2, etc.) that establish a positive feedback loop with proinflammatory cells, promoting new vasculature,

invasion and tumor progression [93]. Indeed, malignant epithelial cells co-injected with senescent fibroblasts have larger and greater numbers of blood vessels compared with controls. Conditioned medium from senescent fibroblasts enhances human umbilical vein endothelial cell invasion [74]. Connective tissue growth factor, CTGF, is another SASP component that facilitates LNCaP human prostate cancer progression by enhancing blood vessel formation [94]. Further, IL-1 α , an endothelial surface adhesion molecule and a SASP factor, is involved in the mechanical contact and transient attachment of circulating cancer cells with microvasculature. This step elicits the trans-vascular penetration and consequent dissemination of cancer cells [95]. Thus, senescent cells are poised to support the development of new vasculature and extracellular remodeling during the metastatic seeding and anchorage of progressing tumors.

3.5. Immune-Suppressive Modulation

Tumor cells engage different immune cells to promote an immunosuppressive environment, which favors metastasis colonization. Among the different immune cell subtypes, myeloid-derived suppressor cells (MDSCs) exert a consistent immunosuppressive action in different organs, including liver, lung, bone and brain [96–98]. MDSCs secrete OPN, (see above), which interferes with CD8⁺ T cell proliferation, thus favoring lung metastasis. CXCR2 signaling in MDSCs and neutrophils reduces CD3⁺ cell infiltration in liver metastasis, mimicking the immune-suppressive effect observed in the lung [99].

In a mouse model that develops premalignant prostatic lesions after the ablation of PTEN, a strong senescence tumoral response progresses to invasive adenocarcinoma [100]. This was linked to an immunosuppressive environment enriched in MDSCs cells and CXCL1/CXCL2, GM-CSF, M-CSF, IL10 and IL13 SASPs factors. Pharmacological inhibition of the immune-suppressive secretory arm of SASP favors an antitumoral microenvironment, which restored inflammatory immune cells and tumor resolution. In the same model, GR1⁺ cells secrete interleukin-1 receptor antagonist (ILRA), protecting a fraction of cancer cells from entering senescence [101]. The immunosuppressive nature of the SASP was also observed in a mouse model of obesity-induced hepatocellular carcinoma. Hepatic stellate cells become senescent after exposure to lipoteichoic acid (LTA) and deoxycholic acid, two obesity-induced gut microbial components. The resultant prostaglandin PGE2 production results in the attenuation of host antitumor immunity and HCC progression [102]. Finally, in colorectal cancer, senescent tumor cells can generate a CXCL12 gradient that inhibits CD8⁺ T cell chemotaxis by orchestrating CXCR4 plasma membrane receptor loss *in vitro* and *in vivo*. Senescent cancer cells also secreted colony-stimulating factor 1 (CSF1), which enhanced monocyte differentiation into M2 macrophages, with known inhibitory properties on CD8⁺ T cell activation [15]. While these data were collected on primary tumor models, this, in principle, can be expected to extend to secondary tissue niches. Importantly, the complexity of the SASP, which is cell type-, time-, and stressor-dependent, is a source of multiple possibilities for metastatic activation and has to be evaluated in the context of the model and disease studied [103].

3.6. Pro-Survival Intrinsic and External Anoikis Signals

Signals that prevent cell death are critical for metastatic cells to colonize new tissues [104]. Resistance to apoptosis is a common feature of many senescent cells [89]. Indeed, one of the earliest strategies for killing senescent cells was developed on the hypothesis that senescent cells were more sensitive to the inhibition of those pro-survival networks compared to non-senescent cells. Senescent cells upregulate the anti-apoptotic proteins BCL-W and BCL-XL, and genetic or pharmacological inhibition of BCL-W and BCL-XL selectively induces apoptosis in senescent cells [105–107]. The *in vivo* administration of ABT-737 eliminates senescent cells in both the lung and epidermis. Lipofuscin, commonly elevated in senescent cells, stimulates the expression of the anti-apoptotic factor Bcl-2, conferring resistance to apoptosis [108]. Another possible mechanism was attributed to the decoy death receptor DCR2, a cell surface receptor elevated in mouse senescent

cells [109]. DCR2 protects senescent cells from immunity-mediated apoptosis, thus blocking the immune surveillance of senescent cells. This receptor is not conserved between mouse and human, but it is likely that human cells are able to develop cell-surface markers with immune-resistance activity, such as DCR2, which would explain their pro-survival tendency. Finally, CXCR4 and its ligand, CXCL12, can promote metastasis by preventing anoikis in cancer cells [13]. Indeed, senescent thyrocytes confer anoikosis resistance to co-cultured thyroid cancer cells via CXCR4-CXCL12. Functional CXCL12 knockdown or the CXCR4 antagonist AMD3100 decreases the survival of cancer cells. This latest discovery underlies the potential impact of senescent cells on the microenvironment and its paracrine survival action, which is extremely important in the context of cancer. An interesting mechanism of anoikis resistance in metastatic cells involves metabolic reprogramming to overcome ATP deficiency. Indeed, metastatic cancer cells secrete creatin kinase in the extracellular space to increase phosphocreatine, which is then imported and exploited as a source of ATP [110]. Thus, both senescent and metastatic cancer cells activate mechanisms that enable survival, allowing for cancers to spread to sites that may otherwise be inhospitable.

4. Metabolic Plasticity

Cancer cells often rely on glycolysis to synthesize the macromolecules required for continued cell division. To maintain this high level of glycolysis, most glucose-derived pyruvate is converted to lactate in the cytoplasm by lactate dehydrogenase (LDH), and secreted into the tumor microenvironment. This allows cancer cells to activate multiple biosynthetic pathways, which provide important building blocks for biomass synthesis and proliferation. This shift occurs even under oxygen-replete conditions with no defects in mitochondrial function, creating a pseudo-hypoxic state known as the Warburg effect [111]. However, cancer cells often adapt their metabolism during their metastatic journey [112], due to different nutrient and oxygen availability in “soil” tissues. Those tissue-specific metabolic features could also determine a priori their hospitability to circulating cancer cells, depending on the metabolic affinity with the primary organ. High levels of oxygen and glucose characterize brain and lung, which promote aerobic glycolysis or oxidative phosphorylation as an adaptive metabolism for energetic metastatic demand. Contrarily, the liver with low oxygen and fluctuating glucose levels relies on creatinine cycle activation to scavenge ATP or beta-oxidation [113]. Metabolic heterogeneity exists even within the same tumor due to variability in genetic alterations, epigenetic regulation, and transcriptional programs [114], further increasing complexity. Some metabolites are shared between primary cancer and metastasis, but others are specific for the metastatic site, and in some contexts, targeting only one of the nutrients that produce these molecules is sufficient to exhibit therapeutic efficacy in mouse models [115]. Thus, metabolism is a potential Achilles heel in the treatment of metastatic cells. Additionally, the large cell size and increased metabolism of polyploid tumor cells may represent a point of fragility specific to the polyploid subpopulation that could be exploited by metabolic targeted therapy.

The activation of glycolysis is also a feature of senescent cells [116–118]. Therapy-induced senescent lymphoma cells show increased glucose conversion to pyruvate, lactate and citrate. Senescent lymphoma cells lacking NF- κ B, a master regulator of proinflammatory features of the SASP, have a muted SASP and more limited glucose consumption [117]. This suggests that most of the metabolic demand in senescent cells is linked to their secretory properties but also to the genetic alteration, like cancer cells. In support of this consideration, p53 and RB, the two tumor suppressors which mediate the major pathways of cellular senescence, drive different metabolic phenotypes in oncogene-induced senescence. While RB stimulates glycolysis, p53 favors the mitochondrial oxidation of pyruvate and fatty acids [119]. Similar to TIS, BRAF^{V600E} oncogene-induced senescent melanoma cells showed an increase in both glucose consumption and pyruvate metabolism [120].

Metabolites such as lactate, pyruvate, glutamine and lipids appear to be crucial metabolites in many steps of the metastatic cascade. The senescent program seems to be tightly connected to metabolism and metabolic stress. For simplicity, we summarized below the

key findings which have an evident impact on senescence and metastasis. For a fully comprehensive perspective on metabolism in cellular senescence, we referred to recent reviews [121,122].

4.1. Pyruvate and Lactate

Pyruvate and lactate in cancer cells are both involved in EMT and ECM degradation, favoring migration. Lactate dehydrogenase A (LDHA) converts lactate in pyruvate, and its inhibition impairs invasion and migration in in vitro assays of renal cell carcinoma (RCC), pancreatic cancer and prostate cancer—and decreased metastasis in an orthotopic renal xenograft model [123–125]. High levels of the monocarboxylate transporter 1 (MCT1), which regulates lactate exchange from the intra- to extracellular space, are linked to a lower survival rate in patients with bladder cancer [126]. However, the radiation of human breast cancer cells induces MCT1 upregulation, lactate efflux, and the activation of NF- κ B associated with senescence [127]. The MCT1-NF- κ B axis promotes pro-invasive EMT in cervix squamous carcinoma, osteosarcoma and breast mammary carcinoma mouse models [128]. These findings suggest overlapping functions for pyruvate and lactate in the context of metastasis and cellular senescence.

4.2. NAD⁺

NAD⁺ is a cofactor for multi-redox pathways and a substrate for different signaling enzymes, and a key factor in tissue homeostasis [129]. Higher NAD⁺/NADH and NADP⁺/NADPH ratios are found in cancer cells compared to their non-transformed counterparts, suggesting the important role of NAD⁺ in their metabolic conversion [130]. Indeed, NAD⁺ is an essential cofactor for GAPDH activity, and lactate production from pyruvate converts NADH into NAD⁺. The upregulation of the NAD⁺ salvage pathway, the main source of NAD⁺ in most cells, is a common feature in many cancer cells, and nicotinamide phosphoribosyl-transferase (NAMPT), the rate-limiting enzyme of this pathway, is elevated in several human tumors including gastric, glioma and colorectal cancer. In many tumors, NAMPT expression correlates with worse prognosis and metastasis [129]. Furthermore, NADH can be a cancer stem cell marker [131].

The relationship between NAD⁺ and senescence is complex. Oncogene-induced senescent human fibroblasts accumulate high levels of intracellular NAD⁺ and NAMPT, which promote parts of the SASP through the activation of NF- κ B [132]. The inhibition of NAMPT also promotes senescence, but without many segments of the SASP [133]. Senescent cells can also promote NAD⁺ decline in aged tissue, through macrophage activation [134]. Aged liver and visceral white adipose tissues accumulate inflammatory M1-like macrophages with enhanced CD38 NADase activity, thereby reducing NAD⁺ levels. Senescent cells within those tissues enhance CD38 overexpression in macrophages through the SASP. Together, these data suggest that NAD⁺ depletion may limit tumorigenesis by limiting both glycolytic activation and the SASP, but potentially at the cost of driving age-related conditions.

4.3. Lipids

Lipids are the primary building blocks of cellular membranes, a major mechanism of energy storage, and the source of multiple cellular signals. Aside from essential fatty acids, most can be synthesized *de novo*, but all can be taken up from the extracellular compartment [135]. Lipids have been functionally implicated in several steps of the metastatic cascade, through distinct mechanisms. First, the overexpression of transmembrane receptors for fatty acid import is a common trait of cancer cells with increased invasiveness and migratory properties. Among these, CD36 is used as an early diagnostic biomarker for metastatic cancers. Metastasis-initiating cells express CD36, and blocking this receptor inhibits metastasis formation in human oral carcinoma and other human cancer types [136]. Further, a study of over 2500 cases of different types of cancers stratified in metastatic versus primary tumors revealed that the CD36 gene was frequently amplified in metastatic

groups and, similarly, poor survival rates correlate with CD36 high-copy numbers [137]. CD36-associated fatty acid uptake is also able to promote EMT in hepatocellular carcinoma cell lines [138], whereas in cervical cancer, the pro-metastatic effect of CD36 was synergistic with TGF β -induced EMT in cell lines [139]. CD36 is rapidly upregulated in multiple cell types in response to replicative, oncogenic and chemical senescence-inducing stimuli [140]. In senescent cells, CD36 is activated by amyloid beta proteins instead of fatty acids themselves. This interaction stimulates NF- κ B-dependent cytokine and chemokine production, leading to senescence onset. Therefore, the CD36 receptor is actively involved in SASP production. While the CD36 amyloid interaction was not evaluated in the context of cancer, it is tempting to speculate its involvement in the invasiveness of CD36+ cancer cells.

Second, de novo fatty acid synthesis contributes to the invasion, migration capacity and colonization of cancer cells. Accordingly, fatty acid synthase (FASN) overexpression increases the peritoneal metastasis of ovarian cancers in mice, and promotes cellular colony formation and metastatic ability in vitro [141]. The inhibition of FASN with the compound orlistate impairs melanoma-induced metastases and angiogenesis in mice [142], and the silencing of FASN attenuates CD44 expression-induced signaling and metastasis formation in colorectal cancer mouse models [143]. FASN was similarly elevated in senescent cells and required for both the cell cycle arrest and SASP production in oncogene-induced senescence [144].

Third, fatty acids can be further processed in the cell; the resulting metabolites are involved not only in metastasis but also in senescence [145], suggesting that saturated fatty acids might be an important substrate for energy production in senescent cells and migratory properties in cancer cells. Indeed, senescent cells can store lipids in the form of triglycerides with incorporated free polyunsaturated fatty acid (PUFA) [146]. PUFA can be further metabolized into oxylipins, which have proinflammatory properties and senescence-regulatory properties [147]. The overexpression of 5-Lipoxygenase (5-LOX), which is known to promote cancer [148], also drives senescence-like growth arrest via a p53/p21-dependent pathway [149]. In cancer, PUFA are known to induce proliferation, apoptosis and angiogenesis [150]. However, their role in metastasis is still in its infancy due to the lack of experimental models which adequately recapitulate the complexity of human cancer, but recently, the intake of ω -6 PUFAs in the diet was shown to enhance the malignancy of tumor cells by the upregulation of pro-tumoral oxylipins (PGs, HETEs, DiHETEs and HODEs) in a murine model of pulmonary squamous cell carcinoma, increasing proliferation, angiogenesis and molecular aggressiveness [151]. Increased oxylipin metabolism was also proposed as a marker for the evaluation of early stage of breast cancer [152]. Taken together, those reports highlight the need for future investigations on the senescence–metastasis axis.

5. Conclusions and Future Directions

Here, we outline the intrinsic and extrinsic plasticity of senescent cells, both as cancer cells and as part of the stroma, supporting all the steps of metastasis development, from invasion to colonization (Figure 3). The extent to which cellular senescence in extra-embryonic contexts recapitulates placenta in cytokine secretion, fusogenic potential, polyploidy and stemness reveals their potential impact on metastasis. Cellular senescence is a stress response, but also a critical step in driving survival advantages in cancer. SASPs evoke several features related to metastasis progression and colonization, which can target cancer cells directly, but also niche components and immune cells, introducing multiple pathways for promoting tumor development. Senescent cells are metabolically active, but also metabolically plastic, and metabolic adaptation is a major rate-limiting step in the metastasis cascade because it defines the metabolic vulnerabilities of cancer cells. Despite this evident connection, many important biological questions remain unanswered. Do senescent cancer cells migrate from primary site to distant organs along with proliferative cancer cells? Are migrating senescent cancer cells heterogeneous in their transcriptional program and secretory production? Do senescent cancer cells undergo metabolic reprogramming and in what contexts? Do senescent cancer cells secrete metabolites that alter

the ability of cancer cells to invade soil tissues? These questions will likely be addressed in coming years by emerging new technological approaches, including spatial transcriptomics at a single-cell resolution and the use of artificial intelligence on datasets from human specimens. This reflects the level of complexity of the role played by cellular senescence in the context of metastasis. Importantly, some metabolites are shared between primary cancer and metastasis, but others are specific to metastatic sites. Findings show that targeting single nutrients that produce these molecules is sufficient to exhibit therapeutic efficacy in mouse models, suggesting that metabolism is likely an Achilles heel in the treatment of metastatic cells. However, further studies are required to assess the functional relevance and significance of metabolic shifts in senescent cancer cells. For polyploid cancer cells, targeting senescence indispensable metabolites could be a new key for the intervention of aging-associated and age-related pathologies, including metastasis. These approaches will facilitate deep insights into the complex biological phenomenon of human metastasis and lead to a better understanding of the heterogeneity of cellular senescence, with the ultimate goal of developing more precise interventions for metastatic cancer.

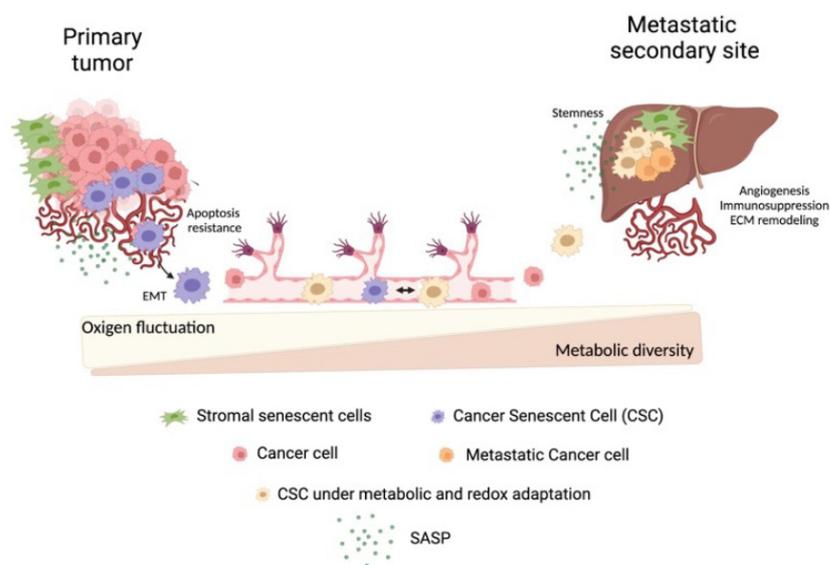


Figure 3. Summary of the intrinsic and extrinsic plasticity of senescent cells.

The progression to deep invasion and metastasis may be fueled by SSCs at the primary and secondary site by paracrine SASP signaling. In the first case, SASP can lead to neo-angiogenesis and confer EMT- and stem-like properties to cancer cells, while in the soil organs, SASP can contribute to establish a permissive niche, being involved in ECM remodeling, immunosuppression and angiogenesis. CSC can detach from the primary tumor and enter in the circulation, in which they survive through their intrinsic resistance to apoptotic signaling and invasive properties of the EMT phenotype. During the journey, senescent cells can undergo a multi-step process of metabolic and environmental adaptation, which ultimately leads to their soil into the metastatic organ. At this site, CSCs could boost non-senescent cancer cells to a more aggressive stem-like state.

Fortunately, the contribution of senescence and the SASP to metastatic invasion offers hope for future therapeutic intervention [153]. This could come in two ways: (1) preventing the metastasis-promoting effects of senescent cells, or (2) eliminating senescent cells so that they cannot promote metastasis. Molecules that inhibit or restrain the SASP, such as rapamycin or metformin, have been shown to prevent cancer progression [154–156]. Molecules that selectively kill senescent cells, called “senolytics”, also show promise as cancer therapeutics. Indeed, one strategy that has been successfully employed in animals is to first render cancer cells senescent using chemotherapeutics [83], PARP inhibitors [157] or CDC7 inhibitors [158], followed by the elimination of these induced senescent cells using senolytic compounds. This “one-two-punch” approach may improve treatment

options where other strategies fail [159]. Senescent cancer cells are antitumoral in the short term, while chronic exposure to the SASP leads to cancer recurrence and prolonged-therapy side effects. How do we select the deleterious senescent cells against the beneficial ones? To avoid the context-dependency issue of senescence-opposing effects, senolytic chimeric antigen receptor (CAR) T cell therapy could be used to selectively target only pathogenic senescent cells. Chimeric receptors that recognize cell-surface proteins specifically upregulated in senescence, such as uPAR-specific CAR T cells, effectively eliminate senescent cells in a lung cancer mouse model [160]. A less cost-effective strategy would be to generate antibody–drug conjugates that combine monoclonal antibodies specific to senescence-surface antigens with toxins [161].

Thus, while many questions currently remain unanswered, the need to dissect senescence heterogeneity in human cancers has become evident. Applying this knowledge holds great potential for opening new avenues in more effective cancer therapies.

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References

1. Celià-Terrassa, T.; Kang, Y. Distinctive Properties of Metastasis-Initiating Cells. *Genes Dev.* **2016**, *30*, 892–908. [[CrossRef](#)]
2. Celià-Terrassa, T.; Kang, Y. Metastatic Niche Functions and Therapeutic Opportunities. *Nat. Cell Biol.* **2018**, *20*, 868–877. [[CrossRef](#)] [[PubMed](#)]
3. Hu, Z.; Ding, J.; Ma, Z.; Sun, R.; Seoane, J.A.; Scott Shaffer, J.; Suarez, C.J.; Berghoff, A.S.; Cremolini, C.; Falcone, A.; et al. Quantitative Evidence for Early Metastatic Seeding in Colorectal Cancer. *Nat. Genet.* **2019**, *51*, 1113–1122. [[CrossRef](#)] [[PubMed](#)]
4. Langley, R.R.; Fidler, I.J. The Seed and Soil Hypothesis Revisited-The Role of Tumor-Stroma Interactions in Metastasis to Different Organs. *Int. J. Cancer* **2011**, *128*, 2527–2535. [[CrossRef](#)] [[PubMed](#)]
5. Gorgoulis, V.; Adams, P.D.; Alimonti, A.; Bennett, D.C.; Bischof, O.; Bishop, C.; Campisi, J.; Collado, M.; Evangelou, K.; Ferbeyre, G.; et al. Cellular Senescence: Defining a Path Forward. *Cell* **2019**, *179*, 813–827. [[CrossRef](#)] [[PubMed](#)]
6. Campisi, J. Senescent Cells, Tumor Suppression, and Organismal Aging: Good Citizens, Bad Neighbors. *Cell* **2005**, *120*, 513–522. [[CrossRef](#)] [[PubMed](#)]
7. Campisi, J. Aging, Cellular Senescence, and Cancer. *Annu. Rev. Physiol.* **2013**, *75*, 685–705. [[CrossRef](#)]
8. Lecot, P.; Alimirah, F.; Desprez, P.Y.; Campisi, J.; Wiley, C. Context-Dependent Effects of Cellular Senescence in Cancer Development. *Br. J. Cancer* **2016**, *114*, 1180–1184. [[CrossRef](#)]
9. Michaloglou, C.; Vredeveld, L.C.W.; Soengas, M.S.; Denoyelle, C.; Kuilman, T.; van der Horst, C.M.A.M.; Majoor, D.M.; Shay, J.W.; Mooi, W.J.; Peeper, D.S. BRAFE600-Associated Senescence-like Cell Cycle Arrest of Human Naevi. *Nature* **2005**, *436*, 720–724. [[CrossRef](#)]
10. Collado, M.; Gil, J.; Efeyan, A.; Guerra, C.; Schuhmacher, A.J.; Barradas, M.; Benguría, A.; Zaballos, A.; Flores, J.M.; Barbacid, M.; et al. Senescence in Premalignant Tumours. *Nature* **2005**, *436*, 642. [[CrossRef](#)]
11. Chen, Z.; Trotman, L.C.; Shaffer, D.; Lin, H.-K.; Dotan, Z.A.; Niki, M.; Koutcher, J.A.; Scher, H.I.; Ludwig, T.; Gerald, W.; et al. Crucial Role of P53-Dependent Cellular Senescence in Suppression of Pten-Deficient Tumorigenesis. *Nature* **2005**, *436*, 725–730. [[CrossRef](#)] [[PubMed](#)]
12. Wyld, L.; Bellantuono, I.; Tchkonja, T.; Morgan, J.; Turner, O.; Foss, F.; George, J.; Danson, S.; Kirkland, J.L. Senescence and Cancer: A Review of Clinical Implications of Senescence and Senotherapies. *Cancers* **2020**, *12*, 2134. [[CrossRef](#)] [[PubMed](#)]
13. Kim, Y.H.; Choi, Y.W.; Lee, J.; Soh, E.Y.; Kim, J.H.; Park, T.J. Senescent Tumor Cells Lead the Collective Invasion in Thyroid Cancer. *Nat. Commun.* **2017**, *8*, 15208. [[CrossRef](#)]
14. Kawaguchi, K.; Komoda, K.; Mikawa, R.; Asai, A.; Sugimoto, M. Cellular Senescence Promotes Cancer Metastasis by Enhancing Soluble E-Cadherin Production. *iScience* **2021**, *24*, 103022. [[CrossRef](#)] [[PubMed](#)]
15. Choi, Y.W.; Kim, Y.H.; Oh, S.Y.; Suh, K.W.; Kim, Y.S.; Lee, G.Y.; Yoon, J.E.; Park, S.S.; Lee, Y.K.; Park, Y.J.; et al. Senescent Tumor Cells Build a Cytokine Shield in Colorectal Cancer. *Adv. Sci.* **2021**, *8*, 2002497. [[CrossRef](#)]
16. Xiao, Z.; Yan, L.; Liang, X.; Wang, H. Progress in Deciphering Trophoblast Cell Differentiation during Human Placentation. *Curr. Opin. Cell Biol.* **2020**, *67*, 86–91. [[CrossRef](#)]
17. D’Souza, A.W.; Wagner, G.P. Malignant Cancer and Invasive Placentation: A Case for Positive Pleiotropy between Endometrial and Malignancy Phenotypes. *Evol. Med. Public Health* **2014**, *2014*, 136–145. [[CrossRef](#)]
18. Rossant, J.; Cross, J.C. Placental development: Lessons from mouse mutants. *Nat. Rev. Genet.* **2001**, *2*, 538–548. [[CrossRef](#)]

19. Dupressoir, A.; Vernochet, C.; Harper, F.; Guégan, J.; Dessen, P.; Pierron, G.; Heidmann, T. A pair of co-opted retroviral envelope syncytin genes is required for formation of the two-layered murine placental syncytiotrophoblast. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, E1164–E1173. [[CrossRef](#)]
20. Chuprin, A.; Gal, H.; Biron-Shental, T.; Biran, A.; Amiel, A.; Rozenblatt, S.; Krizhanovsky, V. Cell Fusion Induced by ERVWE1 or Measles Virus Causes Cellular Senescence. *Genes Dev.* **2013**, *27*, 2356–2366. [[CrossRef](#)]
21. Gal, H.; Lysenko, M.; Stroganov, S.; Vadai, E.; Youssef, S.A.; Tzadikvitch-Geffen, K.; Rotkopf, R.; Biron-Shental, T.; Bruin, A.; Neeman, M.; et al. Molecular Pathways of Senescence Regulate Placental Structure and Function. *EMBO J.* **2019**, *38*, e100849. [[CrossRef](#)] [[PubMed](#)]
22. Singh, V.P.; McKinney, S.; Gerton, J.L. Persistent DNA Damage and Senescence in the Placenta Impacts Developmental Outcomes of Embryos. *Dev. Cell* **2020**, *54*, 333–347.e7. [[CrossRef](#)] [[PubMed](#)]
23. Jones, S.A.; Jenkins, B.J. Recent Insights into Targeting the IL-6 Cytokine Family in Inflammatory Diseases and Cancer. *Nat. Rev. Immunol.* **2018**, *18*, 773–789. [[CrossRef](#)] [[PubMed](#)]
24. Rokavec, M.; Öner, M.G.; Li, H.; Jackstadt, R.; Jiang, L.; Lodygin, D.; Kaller, M.; Horst, D.; Ziegler, P.K.; Schwitalla, S.; et al. IL-6R/STAT3/MiR-34a Feedback Loop Promotes EMT-Mediated Colorectal Cancer Invasion and Metastasis. *J. Clin. Investig.* **2014**, *124*, 1853–1867. [[CrossRef](#)]
25. Wang, L.-H.; Lin, C.-Y.; Liu, S.-C.; Liu, G.-T.; Chen, Y.-L.; Chen, J.-J.; Chan, C.-H.; Lin, T.-Y.; Chen, C.-K.; Xu, G.-H.; et al. CCL5 Promotes VEGF-C Production and Induces Lymphangiogenesis by Suppressing MiR-507 in Human Chondrosarcoma Cells. *Oncotarget* **2016**, *7*, 36896–36908. [[CrossRef](#)] [[PubMed](#)]
26. Wang, D.; Sun, H.; Wei, J.; Cen, B.; DuBois, R.N. CXCL1 Is Critical for Premetastatic Niche Formation and Metastasis in Colorectal Cancer. *Cancer Res.* **2017**, *77*, 3655–3665. [[CrossRef](#)] [[PubMed](#)]
27. Faggioli, F.; Sacco, M.G.; Susani, L.; Montagna, C.; Vezzoni, P. Cell Fusion Is a Physiological Process in Mouse Liver. *Hepatology* **2008**, *48*, 1655–1664. [[CrossRef](#)]
28. Pereira, M.; Petretto, E.; Gordon, S.; Bassett, J.H.D.; Williams, G.R.; Behmoaras, J. Common Signalling Pathways in Macrophage and Osteoclast Multinucleation. *J. Cell Sci.* **2018**, *131*. [[CrossRef](#)]
29. Petrány, M.J.; Millay, D.P. Cell Fusion: Merging Membranes and Making Muscle. *Trends Cell Biol.* **2019**, *29*, 964–973. [[CrossRef](#)]
30. Mortensen, K.; Lichtenberg, J.; Thomsen, P.D.; Larsson, L.I. Spontaneous Fusion between Cancer Cells and Endothelial Cells. *Cell. Mol. Life Sci.* **2004**, *61*, 2125–2131. [[CrossRef](#)]
31. Jacobsen, B.M.; Harrell, J.C.; Jedlicka, P.; Borges, V.F.; Varella-Garcia, M.; Horwitz, K.B. Spontaneous Fusion with, and Transformation of Mouse Stroma by, Malignant Human Breast Cancer Epithelium. *Cancer Res.* **2006**, *66*, 8274–8279. [[CrossRef](#)] [[PubMed](#)]
32. Pawelek, J.M.; Chakraborty, A.K. Fusion of Tumour Cells with Bone Marrow-Derived Cells: A Unifying Explanation for Metastasis. *Nat. Rev. Cancer* **2008**, *8*, 377–386. [[CrossRef](#)] [[PubMed](#)]
33. Harris, H.; Miller, O.J.; Klein, G.; Worst, P.; Tachibana, T. Suppression of Malignancy by Cell Fusion. *Nature* **1969**, *223*, 363–368. [[CrossRef](#)]
34. Duelli, D.M.; Hearn, S.; Myers, M.P.; Lazebnik, Y. A Primate Virus Generates Transformed Human Cells by Fusion. *J. Cell Biol.* **2005**, *171*, 493–503. [[CrossRef](#)] [[PubMed](#)]
35. Reddel, R.R. Senescence: An Antiviral Defense That Is Tumor Suppressive? *Carcinogenesis* **2010**, *31*, 19–26. [[CrossRef](#)] [[PubMed](#)]
36. Larsen, J.M.; Christensen, I.J.; Nielsen, H.J.; Hansen, U.; Bjerregaard, B.; Talts, J.F.; Larsson, L.I. Syncytin Immunoreactivity in Colorectal Cancer: Potential Prognostic Impact. *Cancer Lett.* **2009**, *280*, 44–49. [[CrossRef](#)]
37. Larsson, L.-I.; Holck, S.; Christensen, I.J. Prognostic Role of Syncytin Expression in Breast Cancer. *Human Pathol.* **2007**, *38*, 726–731. [[CrossRef](#)]
38. Strick, R.; Ackermann, S.; Langbein, M.; Swiatek, J.; Schubert, S.W.; Hashemolhosseini, S.; Koscheck, T.; Fasching, P.A.; Schild, R.L.; Beckmann, M.W.; et al. Proliferation and Cell-Cell Fusion of Endometrial Carcinoma Are Induced by the Human Endogenous Retroviral Syncytin-1 and Regulated by TGF- β . *J. Mol. Med.* **2007**, *85*, 23–38. [[CrossRef](#)]
39. Duelli, D.; Lazebnik, Y. Cell-to-Cell Fusion as a Link between Viruses and Cancer. *Nat. Rev. Cancer* **2007**, *7*, 968–976. [[CrossRef](#)]
40. Duelli, D.; Lazebnik, Y. Cell Fusion: A Hidden Enemy? *Cancer Cell* **2003**, *3*, 445–448. [[CrossRef](#)]
41. Derks, W.; Bergmann, O. Polyploidy in Cardiomyocytes. *Circ. Res.* **2020**, *126*, 552–565. [[CrossRef](#)] [[PubMed](#)]
42. Kudryavtsev, B.N.; Kudryavtseva, M.V.; Sakuta, G.A.; Stein, G.I. Human Hepatocyte Polyploidization Kinetics in the Course of Life Cycle. *Virchows Arch. B Cell Pathol. Incl. Mol. Pathol.* **1993**, *64*, 387–393. [[CrossRef](#)] [[PubMed](#)]
43. Faggioli, F.; Vezzoni, P.; Montagna, C. Single-Cell Analysis of Ploidy and Centrosomes Underscores the Peculiarity of Normal Hepatocytes. *PLoS ONE* **2011**, *6*, e26080. [[CrossRef](#)] [[PubMed](#)]
44. Muntean, A.G.; Pang, L.; Poncz, M.; Dowdy, S.F.; Blobel, G.A.; Crispino, J.D. Cyclin D-Cdk4 Is Regulated by GATA-1 and Required for Megakaryocyte Growth and Polyploidization. *Blood* **2007**, *109*, 5199–5207. [[CrossRef](#)]
45. Lee, H.O.; Davidson, J.M.; Duronio, R.J. Endoreplication: Polyploidy with Purpose. *Genes Dev.* **2009**, *23*, 2461–2477. [[CrossRef](#)]
46. Mirzayans, R.; Andrais, B.; Murray, D. Roles of Polyploid/Multinucleated Giant Cancer Cells in Metastasis and Disease Relapse Following Anticancer Treatment. *Cancers* **2018**, *10*, 118. [[CrossRef](#)]
47. Galmarini, C.M.; Falette, N.; Tabone, E.; Levrat, C.; Britten, R.; Voorzanger-Rousselot, N.; Roesch-Gateau, O.; Vanier-Viorner, A.; Puisieux, A.; Dumontet, C. Inactivation of Wild-Type P53 by a Dominant Negative Mutant Renders MCF-7 Cells Resistant to Tubulin-Binding Agent Cytotoxicity. *Br. J. Cancer* **2001**, *85*, 902–908. [[CrossRef](#)]

48. Erenpreisa, J.; Cragg, M.S. Three Steps to the Immortality of Cancer Cells: Senescence, Polyploidy and Self-Renewal. *Cancer Cell Int.* **2013**, *13*, 92. [[CrossRef](#)]
49. Mirzayans, R.; Andrais, B.; Scott, A.; Wang, Y.W.; Murray, D. Ionizing Radiation-Induced Responses in Human Cells with Differing TP53 Status. *Int. J. Mol. Sci.* **2013**, *14*, 22409–22435. [[CrossRef](#)]
50. Amend, S.R.; Torga, G.; Lin, K.C.; KostECKa, L.G.; de Marzo, A.; Austin, R.H.; Pienta, K.J. Polyploid Giant Cancer Cells: Unrecognized Actuators of Tumorigenesis, Metastasis, and Resistance. *Prostate* **2019**, *79*, 1489–1497. [[CrossRef](#)]
51. Zack, T.I.; Schumacher, S.E.; Carter, S.L.; Cherniack, A.D.; Saksena, G.; Tabak, B.; Lawrence, M.S.; Zhang, C.Z.; Wala, J.; Mermel, C.H.; et al. Pan-Cancer Patterns of Somatic Copy Number Alteration. *Nat. Genet.* **2013**, *45*, 1134–1140. [[CrossRef](#)] [[PubMed](#)]
52. Bielski, C.M.; Zehir, A.; Penson, A.V.; Donoghue, M.T.A.; Chatila, W.; Armenia, J.; Chang, M.T.; Schram, A.M.; Jonsson, P.; Bandlamudi, C.; et al. Genome Doubling Shapes the Evolution and Prognosis of Advanced Cancers. *Nat. Genet.* **2018**, *50*, 1189–1195. [[CrossRef](#)]
53. Zhang, S.; Zhou, K.; Luo, X.; Li, L.; Tu, H.C.; Sehgal, A.; Nguyen, L.H.; Zhang, Y.; Gopal, P.; Tarlow, B.D.; et al. The Polyploid State Plays a Tumor-Suppressive Role in the Liver. *Dev. Cell* **2018**, *44*, 447–459.e5. [[CrossRef](#)] [[PubMed](#)]
54. Kalluri, R.; Weinberg, R.A. The Basics of Epithelial-Mesenchymal Transition. *J. Clin. Investig.* **2009**, *119*, 1420–1428. [[CrossRef](#)] [[PubMed](#)]
55. Li, W.; Kang, Y. Probing the Fifty Shades of EMT in Metastasis. *Trends Cancer* **2016**, *2*, 65–67. [[CrossRef](#)] [[PubMed](#)]
56. Tsai, J.H.; Donaher, J.L.; Murphy, D.A.; Chau, S.; Yang, J. Spatiotemporal Regulation of Epithelial-Mesenchymal Transition Is Essential for Squamous Cell Carcinoma Metastasis. *Cancer Cell* **2012**, *22*, 725–736. [[CrossRef](#)] [[PubMed](#)]
57. Lawson, D.A.; Bhakta, N.R.; Kessenbrock, K.; Prummel, K.D.; Yu, Y.; Takai, K.; Zhou, A.; Eyob, H.; Balakrishnan, S.; Wang, C.Y.; et al. Single-Cell Analysis Reveals a Stem-Cell Program in Human Metastatic Breast Cancer Cells. *Nature* **2015**, *526*, 131–135. [[CrossRef](#)]
58. Diepenbruck, M.; Christofori, G. Epithelial-Mesenchymal Transition (EMT) and Metastasis: Yes, No, Maybe? *Curr. Opin. Cell Biol.* **2016**, *43*, 7–13. [[CrossRef](#)]
59. Hanahan, D.; Weinberg, R.A. Hallmarks of Cancer: The next Generation. *Cell* **2011**, *144*, 646–674. [[CrossRef](#)]
60. Esposito, M.; Mondal, N.; Greco, T.M.; Wei, Y.; Spadazzi, C.; Lin, S.C.; Zheng, H.; Cheung, C.; Magnani, J.L.; Lin, S.H.; et al. Bone Vascular Niche E-Selectin Induces Mesenchymal–Epithelial Transition and Wnt Activation in Cancer Cells to Promote Bone Metastasis. *Nat. Cell Biol.* **2019**, *21*, 627–639. [[CrossRef](#)]
61. Ombrato, L.; Malanchi, I. The EMT Universe: Space between Cancer Cell Dissemination and Metastasis Initiation. *Crit. Rev. Oncog.* **2014**, *19*, 349–361. [[CrossRef](#)] [[PubMed](#)]
62. Morrison, S.J.; Spradling, A.C. Stem Cells and Niches: Mechanisms That Promote Stem Cell Maintenance throughout Life. *Cell* **2008**, *132*, 598–611. [[CrossRef](#)] [[PubMed](#)]
63. Was, H.; Barszcz, K.; Czarnecka, J.; Kowalczyk, A.; Bernas, T.; Uzarowska, E.; Koza, P.; Klejman, A.; Piwocka, K.; Kaminska, B.; et al. Bafilomycin A1 Triggers Proliferative Potential of Senescent Cancer Cells in Vitro and in NOD/SCID Mice. *Oncotarget* **2017**, *8*, 9303–9322. [[CrossRef](#)] [[PubMed](#)]
64. Erenpreisa, J. Release of mitotic descendants by giant cells from irradiated burkitt’s lymphoma cell lines. *Cell Biol. Int.* **2000**, *24*, 635–648. [[CrossRef](#)] [[PubMed](#)]
65. Niu, N.; Mercado-Uribe, I.; Liu, J. Dedifferentiation into Blastomere-like Cancer Stem Cells via Formation of Polyploid Giant Cancer Cells. *Oncogene* **2017**, *36*, 4887–4900. [[CrossRef](#)]
66. Canino, C.; Mori, F.; Cambria, A.; Diamantini, A.; Germoni, S.; Alessandrini, G.; Borsellino, G.; Galati, R.Z.; Battistini, L.; Blandino, R.; et al. SASP Mediates Chemoresistance and Tumor-Initiating-Activity of Mesothelioma Cells. *Oncogene* **2012**, *31*, 3148–3163. [[CrossRef](#)]
67. Milanovic, M.; Fan, D.N.Y.; Belenki, D.; Däbritz, J.H.M.; Zhao, Z.; Yu, Y.; Dörr, J.R.; Dimitrova, L.; Lenze, D.; Monteiro Barbosa, I.A.; et al. Senescence-Associated Reprogramming Promotes Cancer Stemness. *Nature* **2018**, *553*, 96–100. [[CrossRef](#)]
68. Gerashchenko, B.I.; Salmina, K.; Eglitis, J.; Huna, A.; Grjunberga, V.; Erenpreisa, J. Disentangling the Aneuploidy and Senescence Paradoxes: A Study of Triploid Breast Cancers Non-Responsive to Neoadjuvant Therapy. *Histochem. Cell Biol.* **2016**, *145*, 497–508. [[CrossRef](#)]
69. Coppé, J.P.; Patil, C.K.; Rodier, F.; Sun, Y.; Muñoz, D.P.; Goldstein, J.; Nelson, P.S.; Desprez, P.Y.; Campisi, J. Senescence-Associated Secretory Phenotypes Reveal Cell-Nonautonomous Functions of Oncogenic RAS and the P53 Tumor Suppressor. *PLoS Biol.* **2008**, *6*, e301. [[CrossRef](#)]
70. Tato-Costa, J.; Casimiro, S.; Pacheco, T.; Pires, R.; Fernandes, A.; Alho, I.; Pereira, P.; Costa, P.; Castelo, H.B.; Ferreira, J.; et al. Therapy-Induced Cellular Senescence Induces Epithelial-to-Mesenchymal Transition and Increases Invasiveness in Rectal Cancer. *Clin. Colorectal. Cancer* **2016**, *15*, 170–178.e3. [[CrossRef](#)]
71. Krtolica, A.; Parrinello, S.; Lockett, S.; Desprez, P.-Y.; Campisi, J. Senescent Fibroblasts Promote Epithelial Cell Growth and Tumorigenesis: A Link between Cancer and Aging. *Proc. Natl. Acad. Sci. USA* **2001**, *98*, 12072–12077. [[CrossRef](#)] [[PubMed](#)]
72. Parrinello, S.; Coppe, J.P.; Krtolica, A.; Campisi, J. Stromal-Epithelial Interactions in Aging and Cancer: Senescent Fibroblasts Alter Epithelial Cell Differentiation. *J. Cell Sci.* **2005**, *118*, 485–496. [[CrossRef](#)] [[PubMed](#)]
73. Coppé, J.P.; Patil, C.K.; Rodier, F.; Krtolica, A.; Beauséjour, C.M.; Parrinello, S.; Hodgson, J.G.; Chin, K.; Desprez, P.Y.; Campisi, J. A Human-like Senescence-Associated Secretory Phenotype Is Conserved in Mouse Cells Dependent on Physiological Oxygen. *PLoS ONE* **2010**, *5*, e9188. [[CrossRef](#)] [[PubMed](#)]

74. Coppe, J.P.; Kauser, K.; Campisi, J.; Beauséjour, C.M. Secretion of Vascular Endothelial Growth Factor by Primary Human Fibroblasts at Senescence. *J. Biol. Chem.* **2006**, *281*, 29568–29574. [[CrossRef](#)]
75. Pazolli, E.; Luo, X.; Brehm, S.; Carbery, K.; Chung, J.J.; Prior, J.L.; Doherty, J.; Demehri, S.; Salavaggione, L.; Piwnica-Worms, D.; et al. Senescent Stromal-Derived Osteopontin Promotes Preneoplastic Cell Growth. *Cancer Res.* **2009**, *69*, 1230–1239. [[CrossRef](#)]
76. Jia, R.; Liang, Y.; Chen, R.; Liu, G.; Wang, H.; Tang, M.; Zhou, X.; Wang, H.; Yang, Y.; Wei, H.; et al. Osteopontin Facilitates Tumor Metastasis by Regulating Epithelial–Mesenchymal Plasticity. *Cell Death Dis.* **2016**, *7*, e2564. [[CrossRef](#)]
77. Sahai, E.; Astsaturov, I.; Cukierman, E.; DeNardo, D.G.; Egeblad, M.; Evans, R.M.; Fearon, D.; Greten, F.R.; Hingorani, S.R.; Hunter, T.; et al. A Framework for Advancing Our Understanding of Cancer-Associated Fibroblasts. *Nat. Rev. Cancer* **2020**, *20*, 174–186. [[CrossRef](#)]
78. O’Connell, J.T.; Sugimoto, H.; Cooke, V.G.; MacDonald, B.A.; Mehta, A.I.; LeBleu, V.S.; Dewar, R.; Rocha, R.M.; Brentani, R.R.; Resnick, M.B.; et al. VEGF-A and Tenascin-C Produced by S100A4 + Stromal Cells Are Important for Metastatic Colonization. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 16002–16007. [[CrossRef](#)]
79. Malanchi, I.; Santamaria-Martinez, A.; Susanto, E.; Peng, H.; Lehr, H.A.; Delaloye, J.F.; Huelsken, J. Interactions between Cancer Stem Cells and Their Niche Govern Metastatic Colonization. *Nature* **2012**, *481*, 85–91. [[CrossRef](#)]
80. Basisty, N.; Kale, A.; Jeon, O.H.; Kuehnemann, C.; Payne, T.; Rao, C.; Holtz, A.; Shah, S.; Sharma, V.; Ferrucci, L.; et al. A Proteomic Atlas of Senescence-Associated Secretomes for Aging Biomarker Development. *PLoS Biol.* **2020**, *18*, e3000599. [[CrossRef](#)]
81. Calon, A.; Espinet, E.; Palomo-Ponce, S.; Tauriello, D.V.F.; Iglesias, M.; Céspedes, M.V.; Sevillano, M.; Nadal, C.; Jung, P.; Zhang, X.H.F.; et al. Dependency of Colorectal Cancer on a TGF- β -Driven Program in Stromal Cells for Metastasis Initiation. *Cancer Cell* **2012**, *22*, 571–584. [[CrossRef](#)] [[PubMed](#)]
82. Widjaja, A.A.; Chothani, S.; Viswanathan, S.; Goh, J.W.T.; Lim, W.-W.; Cook, S.A. IL11 Stimulates IL33 Expression and Proinflammatory Fibroblast Activation across Tissues. *Int. J. Mol. Sci.* **2022**, *23*, 8900. [[CrossRef](#)] [[PubMed](#)]
83. Demaria, M.; O’Leary, M.N.; Chang, J.; Shao, L.; Liu, S.; Alimirah, F.; Koenig, K.; Le, C.; Mitin, N.; Deal, A.M.; et al. Cellular Senescence Promotes Adverse Effects of Chemotherapy and Cancer Relapse. *Cancer Discov.* **2017**, *7*, 165–176. [[CrossRef](#)] [[PubMed](#)]
84. Angelini, P.D.; Zacarias Fluck, M.F.; Pedersen, K.; Parra-Palau, J.L.; Guiu, M.; Morales, C.B.; Vicario, R.; Luque-García, A.; Navalpotro, N.P.; Giral, J.; et al. Constitutive HER2 Signaling Promotes Breast Cancer Metastasis through Cellular Senescence. *Cancer Res.* **2013**, *73*, 450–458. [[CrossRef](#)]
85. Sahai, E. Illuminating the Metastatic Process. *Nat. Rev. Cancer* **2007**, *7*, 737–749. [[CrossRef](#)]
86. Seguin, L.; Desgrosellier, J.S.; Weis, S.M.; Cheresch, D.A. Integrins and Cancer: Regulators of Cancer Stemness, Metastasis, and Drug Resistance. *Trends Cell Biol.* **2015**, *25*, 234–240. [[CrossRef](#)]
87. Costa-Silva, B.; Aiello, N.M.; Ocean, A.J.; Singh, S.; Zhang, H.; Thakur, B.K.; Becker, A.; Hoshino, A.; Mark, M.T.; Molina, H.; et al. Pancreatic Cancer Exosomes Initiate Pre-Metastatic Niche Formation in the Liver. *Nat. Cell Biol.* **2015**, *17*, 816–826. [[CrossRef](#)]
88. Murgai, M.; Ju, W.; Eason, M.; Kline, J.; Beury, D.W.; Kaczanowska, S.; Miettinen, M.M.; Kruhlik, M.; Lei, H.; Shern, J.F.; et al. KLF4-Dependent Perivascular Cell Plasticity Mediates Pre-Metastatic Niche Formation and Metastasis. *Nat. Med.* **2017**, *23*, 1176–1190. [[CrossRef](#)]
89. Soto-Gamez, A.; Quax, W.J.; Demaria, M. Regulation of Survival Networks in Senescent Cells: From Mechanisms to Interventions. *J. Mol. Biol.* **2019**, *431*, 2629–2643. [[CrossRef](#)]
90. Liu, D.; Hornsby, P.J. Senescent Human Fibroblasts Increase the Early Growth of Xenograft Tumors via Matrix Metalloproteinase Secretion. *Cancer Res.* **2007**, *67*, 3117–3126. [[CrossRef](#)]
91. Tsai, K.K.C.; Yao, E.; Chuang, Y.; Little, J.B.; Yuan, Z.-M. Cellular Mechanisms for Low-Dose Ionizing Radiation-Induced Perturbation of the Breast Tissue Microenvironment. *Cancer Res.* **2005**, *65*, 6734–6744. [[CrossRef](#)] [[PubMed](#)]
92. Malaquin, N.; Vercamer, C.; Bouali, F.; Martien, S.; Deruy, E.; Wernert, N.; Chwastyniak, M.; Pinet, F.; Abbadie, C.; Pourtier, A. Senescent Fibroblasts Enhance Early Skin Carcinogenic Events via a Paracrine MMP-PAR-1 Axis. *PLoS ONE* **2013**, *8*, e63607. [[CrossRef](#)] [[PubMed](#)]
93. Tonini, T.; Rossi, F.; Claudio, P.P. Molecular Basis of Angiogenesis and Cancer. *Oncogene* **2003**, *22*, 6549–6556. [[CrossRef](#)] [[PubMed](#)]
94. Yang, F.; Tuxhorn, J.A.; Ressler, S.J.; McAlhany, S.J.; Dang, T.D.; Rowley, D.R. Stromal Expression of Connective Tissue Growth Factor Promotes Angiogenesis and Prostate Cancer Tumorigenesis. *Cancer Res.* **2005**, *65*, 8887–8895. [[CrossRef](#)] [[PubMed](#)]
95. Gelfo, V.; Romaniello, D.; Mazzeschi, M.; Sgarzi, M.; Grilli, G.; Morselli, A.; Manzan, B.; Rihawi, K.; Lauriola, M. Roles of Il-1 in Cancer: From Tumor Progression to Resistance to Targeted Therapies. *Int. J. Mol. Sci.* **2020**, *21*, 6009. [[CrossRef](#)] [[PubMed](#)]
96. Condamine, T.; Ramachandran, I.; Youn, J.-I.; Gabrilovich, D.I. Regulation of Tumor Metastasis by Myeloid-Derived Suppressor Cells. *Annu. Rev. Med.* **2015**, *66*, 97–110. [[CrossRef](#)]
97. Marvel, D.; Gabrilovich, D.I. Myeloid-Derived Suppressor Cells in the Tumor Microenvironment: Expect the Unexpected. *J. Clin. Invest.* **2015**, *125*, 3356–3364. [[CrossRef](#)]
98. Liu, Y.; Kosaka, A.; Ikeura, M.; Kohanbash, G.; Fellows-Mayle, W.; Snyder, L.A.; Okada, H. Premetastatic Soil and Prevention of Breast Cancer Brain Metastasis. *Neuro. Oncol.* **2013**, *15*, 891–903. [[CrossRef](#)]
99. Sangaletti, S.; Tripodo, C.; Sandri, S.; Torselli, I.; Vitali, C.; Ratti, C.; Botti, L.; Burocchi, A.; Porcasi, R.; Tomirotti, A.; et al. Osteopontin Shapes Immunosuppression in the Metastatic Niche. *Cancer Res.* **2014**, *74*, 4706–4719. [[CrossRef](#)]
100. Toso, A.; Revandkar, A.; DiMitri, D.; Guccini, I.; Proietti, M.; Sarti, M.; Pinton, S.; Zhang, J.; Kalathur, M.; Civenni, G.; et al. Enhancing Chemotherapy Efficacy in Pten-Deficient Prostate Tumors by Activating the Senescence-Associated Antitumor Immunity. *Cell Rep.* **2014**, *9*, 75–89. [[CrossRef](#)]

101. di Mitri, D.; Toso, A.; Chen, J.J.; Sarti, M.; Pinton, S.; Jost, T.R.; D'Antuono, R.; Montani, E.; Garcia-Escudero, R.; Guccini, I.; et al. Tumour-Infiltrating Gr-1 + Myeloid Cells Antagonize Senescence in Cancer. *Nature* **2014**, *515*, 134–137. [[CrossRef](#)] [[PubMed](#)]
102. Loo, T.M.; Kamachi, F.; Watanabe, Y.; Yoshimoto, S.; Kanda, H.; Arai, Y.; Nakajima-Takagi, Y.; Iwama, A.; Koga, T.; Sugimoto, Y.; et al. Gut Microbiota Promotes Obesity-Associated Liver Cancer through Pge2-Mediated Suppression of Antitumor Immunity. *Cancer Discov.* **2017**, *7*, 522–538. [[CrossRef](#)]
103. Faget, D.V.; Ren, Q.; Stewart, S.A. Unmasking Senescence: Context-Dependent Effects of SASP in Cancer. *Nat. Rev. Cancer* **2019**, *19*, 439–453. [[CrossRef](#)] [[PubMed](#)]
104. Massagué, J.; Obenauf, A.C. Metastatic Colonization by Circulating Tumour Cells. *Nature* **2016**, *529*, 298–306. [[CrossRef](#)]
105. Yosef, R.; Pilpel, N.; Tokarsky-Amiel, R.; Biran, A.; Ovadya, Y.; Cohen, S.; Vadai, E.; Dassa, L.; Shahar, E.; Condiotti, R.; et al. Directed Elimination of Senescent Cells by Inhibition of BCL-W and BCL-XL. *Nat. Commun.* **2016**, *7*, 11190. [[CrossRef](#)]
106. Zhu, Y.; Tchkonja, T.; Fuhrmann-Stroissnigg, H.; Dai, H.M.; Ling, Y.Y.; Stout, M.B.; Pirtskhalava, T.; Giorgadze, N.; Johnson, K.O.; Giles, C.B.; et al. Identification of a Novel Senolytic Agent, Navitoclax, Targeting the Bcl-2 Family of Anti-Apoptotic Factors. *Aging Cell* **2016**, *15*, 428–435. [[CrossRef](#)]
107. Chang, J.; Wang, Y.; Shao, L.; Laberge, R.M.; Demaria, M.; Campisi, J.; Janakiraman, K.; Sharpless, N.E.; Ding, S.; Feng, W.; et al. Clearance of Senescent Cells by ABT263 Rejuvenates Aged Hematopoietic Stem Cells in Mice. *Nat. Med.* **2016**, *22*, 78–83. [[CrossRef](#)]
108. McHugh, D.; Gil, J. Senescence and Aging: Causes, Consequences, and Therapeutic Avenues. *J. Cell Biol.* **2018**, *217*, 65–77. [[CrossRef](#)] [[PubMed](#)]
109. Sagiv, A.; Biran, A.; Yon, M.; Simon, J.; Lowe, S.W.; Krizhanovsky, V. Granule Exocytosis Mediates Immune Surveillance of Senescent Cells. *Oncogene* **2013**, *32*, 1971–1977. [[CrossRef](#)] [[PubMed](#)]
110. Loo, J.M.; Scherl, A.; Nguyen, A.; Man, F.Y.; Weinberg, E.; Zeng, Z.; Saltz, L.; Paty, P.B.; Tavazoie, S.F. Extracellular Metabolic Energetics Can Promote Cancer Progression. *Cell* **2015**, *160*, 393–406. [[CrossRef](#)]
111. Liberti, M.V.; Locasale, J.W. The Warburg Effect: How Does It Benefit Cancer Cells? *Trends Biochem. Sci.* **2016**, *41*, 211–218. [[CrossRef](#)] [[PubMed](#)]
112. Weber, G.F. Metabolism in Cancer Metastasis. *Cancer Lett.* **2008**, *270*, 181–190. [[CrossRef](#)] [[PubMed](#)]
113. Dupuy, F.; Tabariès, S.; Andrzejewski, S.; Dong, Z.; Blagih, J.; Annis, M.G.; Omeroglu, A.; Gao, D.; Leung, S.; Amir, E.; et al. PDK1-Dependent Metabolic Reprogramming Dictates Metastatic Potential in Breast Cancer. *Cell Metab.* **2015**, *22*, 577–589. [[CrossRef](#)] [[PubMed](#)]
114. Nabi, K.; Le, A. The Intratumoral Heterogeneity of Cancer Metabolism. *Adv. Exp. Med. Biol.* **2018**, *1063*, 131–145. [[PubMed](#)]
115. Tarragó-Celada, J.; Cascante, M. Targeting the Metabolic Adaptation of Metastatic Cancer. *Cancers* **2021**, *13*, 1641. [[CrossRef](#)]
116. Chen, J.; Guccini, I.; di Mitri, D.; Brina, D.; Revandkar, A.; Sarti, M.; Pasquini, E.; Alajati, A.; Pinton, S.; Losa, M.; et al. Compartmentalized Activities of the Pyruvate Dehydrogenase Complex Sustain Lipogenesis in Prostate Cancer. *Nat. Genet.* **2018**, *50*, 219–228. [[CrossRef](#)]
117. Dörr, J.R.; Yu, Y.; Milanovic, M.; Beuster, G.; Zasada, C.; Däbritz, J.H.M.; Lisec, J.; Lenze, D.; Gerhardt, A.; Schleicher, K.; et al. Synthetic Lethal Metabolic Targeting of Cellular Senescence in Cancer Therapy. *Nature* **2013**, *501*, 421–425. [[CrossRef](#)]
118. Kaplon, J.; Zheng, L.; Meissl, K.; Chaneton, B.; Selivanov, V.A.; MacKay, G.; van der Burg, S.H.; Verdegaal, E.M.E.; Cascante, M.; Shlomi, T.; et al. A Key Role for Mitochondrial Gatekeeper Pyruvate Dehydrogenase in Oncogene-Induced Senescence. *Nature* **2013**, *498*, 109–112. [[CrossRef](#)]
119. Takebayashi, S.I.; Tanaka, H.; Hino, S.; Nakatsu, Y.; Igata, T.; Sakamoto, A.; Narita, M.; Nakao, M. Retinoblastoma Protein Promotes Oxidative Phosphorylation through Upregulation of Glycolytic Genes in Oncogene-Induced Senescent Cells. *Aging Cell* **2015**, *14*, 689–697. [[CrossRef](#)]
120. Olenchock, B.A.; vander Heiden, M.G. XPyruvate as a Pivot Point for Oncogene-Induced Senescence. *Cell* **2013**, *153*, 1429. [[CrossRef](#)]
121. Wiley, C.D.; Campisi, J. From Ancient Pathways to Aging Cells-Connecting Metabolism and Cellular Senescence. *Cell Metab.* **2016**, *23*, 1013–1021. [[CrossRef](#)] [[PubMed](#)]
122. Wiley, C.D.; Campisi, J. The Metabolic Roots of Senescence: Mechanisms and Opportunities for Intervention. *Nat. Metab.* **2021**, *3*, 1290–1301. [[CrossRef](#)] [[PubMed](#)]
123. Xian, Z.Y.; Liu, J.M.; Chen, Q.K.; Chen, H.Z.; Ye, C.J.; Xue, J.; Yang, H.Q.; Li, J.L.; Liu, X.F.; Kuang, S.J. Inhibition of LDHA Suppresses Tumor Progression in Prostate Cancer. *Tumor. Biology* **2015**, *36*, 8093–8100. [[CrossRef](#)] [[PubMed](#)]
124. He, T.-L.; Zhang, Y.-J.; Jiang, H.; Li, X.-H.; Zhu, H.; Zheng, K.-L. The C-Myc-LDHA Axis Positively Regulates Aerobic Glycolysis and Promotes Tumor Progression in Pancreatic Cancer. *Med. Oncol.* **2015**, *32*, 187. [[CrossRef](#)]
125. Zhao, J.; Huang, X.; Xu, Z.; Dai, J.; He, H.; Zhu, Y.; Wang, H. LDHA Promotes Tumor Metastasis by Facilitating Epithelial-Mesenchymal Transition in Renal Cell Carcinoma. *Mol. Med. Rep.* **2017**, *16*, 8335–8344. [[CrossRef](#)]
126. Zhang, G.; Zhang, Y.; Dong, D.; Wang, F.; Ma, X.; Guan, F.; Sun, L. MCT1 Regulates Aggressive and Metabolic Phenotypes in Bladder Cancer. *J. Cancer* **2018**, *9*, 2492–2501. [[CrossRef](#)]
127. Liao, E.C.; Hsu, Y.T.; Chuah, Q.Y.; Lee, Y.J.; Hu, J.Y.; Huang, T.C.; Yang, P.M.; Chiu, S.J. Radiation Induces Senescence and a Bystander Effect through Metabolic Alterations. *Cell Death Dis.* **2014**, *5*, e1255. [[CrossRef](#)]

128. Payen, V.L.; Hsu, M.Y.; Rädercke, K.S.; Wyart, E.; Vazeille, T.; Bouzin, C.; Porporato, P.E.; Sonveaux, P. Monocarboxylate Transporter MCT1 Promotes Tumor Metastasis Independently of Its Activity as a Lactate Transporter. *Cancer Res.* **2017**, *77*, 5591–5601. [[CrossRef](#)]
129. Navas, L.E.; Carnero, A. NAD⁺ Metabolism, Stemness, the Immune Response, and Cancer. *Signal. Transduct. Target. Ther.* **2021**, *6*. [[CrossRef](#)]
130. da Veiga Moreira, J.; Hamraz, M.; Abolhassani, M.; Bigan, E.; Pérès, S.; Paulevé, L.; Nogueira, M.L.; Steyaert, J.M.; Schwartz, L. The Redox Status of Cancer Cells Supports Mechanisms behind the Warburg Effect. *Metabolites* **2016**, *6*, 33. [[CrossRef](#)]
131. Bonuccelli, G.; de Francesco, E.M.; de Boer, R.; Tanowitz, H.B.; Lisanti, M.P. NADH Autofluorescence, a New Metabolic Biomarker for Cancer Stem Cells: Identification of Vitamin C and CAPE as Natural Products Targeting “Stemness”. *Oncotarget* **2017**, *8*, 20667–20678. [[CrossRef](#)] [[PubMed](#)]
132. Nacarelli, T.; Lau, L.; Fukumoto, T.; Zundell, J.; Fatkhutdinov, N.; Wu, S.; Aird, K.M.; Iwasaki, O.; Kossenkov, A.V.; Schultz, D.; et al. NAD⁺ Metabolism Governs the Proinflammatory Senescence-Associated Secretome. *Nat. Cell Biol.* **2019**, *21*, 397–407. [[CrossRef](#)] [[PubMed](#)]
133. Wiley, C.D.; Velarde, M.C.; Lecot, P.; Liu, S.; Sarnoski, E.A.; Freund, A.; Shirakawa, K.; Lim, H.W.; Davis, S.S.; Ramanathan, A.; et al. Mitochondrial Dysfunction Induces Senescence with a Distinct Secretory Phenotype. *Cell Metab.* **2016**, *23*, 303–314. [[CrossRef](#)] [[PubMed](#)]
134. Covarrubias, A.J.; Kale, A.; Perrone, R.; Lopez-Dominguez, J.A.; Pisco, A.O.; Kasler, H.G.; Schmidt, M.S.; Heckenbach, I.; Kwok, R.; Wiley, C.D.; et al. Senescent Cells Promote Tissue NAD⁺ Decline during Ageing via the Activation of CD38⁺ Macrophages. *Nat. Metab.* **2020**, *2*, 1265–1283. [[CrossRef](#)] [[PubMed](#)]
135. Koundouros, N.; Poulogiannis, G. Reprogramming of Fatty Acid Metabolism in Cancer. *Br. J. Cancer* **2020**, *122*, 4–22. [[CrossRef](#)]
136. Pascual, G.; Avgustinova, A.; Mejetta, S.; Martín, M.; Castellanos, A.; Attolini, C.S.O.; Berenguer, A.; Prats, N.; Toll, A.; Hueto, J.A.; et al. Targeting Metastasis-Initiating Cells through the Fatty Acid Receptor CD36. *Nature* **2017**, *541*, 41–45. [[CrossRef](#)]
137. Nath, A.; Chan, C. Genetic Alterations in Fatty Acid Transport and Metabolism Genes Are Associated with Metastatic Progression and Poor Prognosis of Human Cancers. *Sci. Rep.* **2016**, *6*, srep18669. [[CrossRef](#)]
138. Nath, A.; Li, I.; Roberts, L.R.; Chan, C. Elevated Free Fatty Acid Uptake via CD36 Promotes Epithelial-Mesenchymal Transition in Hepatocellular Carcinoma. *Sci. Rep.* **2015**, *5*, 14752. [[CrossRef](#)]
139. Deng, M.; Cai, X.; Long, L.; Xie, L.; Ma, H.; Zhou, Y.; Liu, S.; Zeng, C. CD36 Promotes the Epithelial-Mesenchymal Transition and Metastasis in Cervical Cancer by Interacting with TGF- β . *J. Transl. Med.* **2019**, *17*, 352. [[CrossRef](#)]
140. Chong, M.; Yin, T.; Chen, R.; Xiang, H.; Yuan, L.; Ding, Y.; Pan, C.C.; Tang, Z.; Alexander, P.B.; Li, Q.; et al. CD 36 Initiates the Secretory Phenotype during the Establishment of Cellular Senescence. *EMBO Rep.* **2018**, *19*, e45274. [[CrossRef](#)]
141. Jiang, L.; Wang, H.; Li, J.; Fang, X.; Pan, H.; Yuan, X.; Zhang, P. Up-Regulated FASN Expression Promotes Transcoelomic Metastasis of Ovarian Cancer Cell through Epithelial-Mesenchymal Transition. *Int. J. Mol. Sci.* **2014**, *15*, 11539–11554. [[CrossRef](#)] [[PubMed](#)]
142. Seguin, F.; Carvalho, M.A.; Bastos, D.C.; Agostini, M.; Zecchin, K.G.; Alvarez-Flores, M.P.; Chudzinski-Tavassi, A.M.; Coletta, R.D.; Graner, E. The Fatty Acid Synthase Inhibitor Orlistat Reduces Experimental Metastases and Angiogenesis in B16-F10 Melanomas. *Br. J. Cancer* **2012**, *107*, 977–987. [[CrossRef](#)] [[PubMed](#)]
143. Zaytseva, Y.Y.; Rychahou, P.G.; Gulhati, P.; Elliott, V.A.; Mustain, W.C.; O’Connor, K.; Morris, A.J.; Sunkara, M.; Weiss, H.L.; Lee, E.Y.; et al. Inhibition of Fatty Acid Synthase Attenuates CD44-Associated Signaling and Reduces Metastasis in Colorectal Cancer. *Cancer Res.* **2012**, *72*, 1504–1517. [[CrossRef](#)] [[PubMed](#)]
144. Fafián-Labora, J.; Carpintero-Fernández, P.; Jordan, S.J.D.; Shikh-Bahaei, T.; Abdullah, S.M.; Mahenthiran, M.; Rodríguez-Navarro, J.A.; Niklison-Chirou, M.V.; O’Loghlen, A. FASN Activity Is Important for the Initial Stages of the Induction of Senescence. *Cell Death Dis.* **2019**, *10*, 318. [[CrossRef](#)] [[PubMed](#)]
145. Flor, A.C.; Wolfgeher, D.; Wu, D.; Kron, S.J. A Signature of Enhanced Lipid Metabolism, Lipid Peroxidation and Aldehyde Stress in Therapy-Induced Senescence. *Cell Death Discov.* **2017**, *3*, 17075. [[CrossRef](#)] [[PubMed](#)]
146. Das, U.N. “Cell Membrane Theory of Senescence” and the Role of Bioactive Lipids in Aging, and Aging Associated Diseases and Their Therapeutic Implications. *Biomolecules* **2021**, *11*, 241. [[CrossRef](#)]
147. Wiley, C.D.; Sharma, R.; Davis, S.S.; Lopez-Dominguez, J.A.; Mitchell, K.P.; Wiley, S.; Alimirah, F.; Kim, D.E.; Payne, T.; Rosko, A.; et al. Oxylipin Biosynthesis Reinforces Cellular Senescence and Allows Detection of Senolysis. *Cell Metab.* **2021**, *33*, 1124–1136.e5. [[CrossRef](#)]
148. Wisastra, R.; Dekker, F.J. Inflammation, Cancer and Oxidative Lipoxygenase Activity Are Intimately Linked. *Cancers* **2014**, *6*, 1500–1521. [[CrossRef](#)]
149. Catalano, A.; Rodilossi, S.; Caprari, P.; Coppola, V.; Procopio, A. 5-Lipoxygenase Regulates Senescence-like Growth Arrest by Promoting ROS-Dependent P53 Activation. *EMBO J.* **2005**, *24*, 170–179. [[CrossRef](#)]
150. Azrad, M.; Turgeon, C.; Demark-Wahnefried, W. Current Evidence Linking Polyunsaturated Fatty Acids with Cancer Risk and Progression. *Front. Oncol.* **2013**, *3*, 224. [[CrossRef](#)]
151. Montecillo-Aguado, M.; Tirado-Rodríguez, B.; Antonio-Andres, G.; Morales-Martinez, M.; Tong, Z.; Yang, J.; Hammock, B.D.; Hernandez-Pando, R.; Huerta-Yepez, S. Omega-6 Polyunsaturated Fatty Acids Enhance Tumor Aggressiveness in Experimental Lung Cancer Model: Important Role of Oxylipins. *Int. J. Mol. Sci.* **2022**, *23*, 6179. [[CrossRef](#)] [[PubMed](#)]

152. Chistyakov, D.V.; Guryleva, M.V.; Stepanova, E.S.; Makarenkova, L.M.; Ptitsyna, E.V.; Goriainov, S.V.; Nikolskaya, A.I.; Astakhova, A.A.; Klimentenko, A.S.; Bezborodova, O.A.; et al. Multi-Omics Approach Points to the Importance of Oxylipins Metabolism in Early-Stage Breast Cancer. *Cancers* **2022**, *14*, 2041. [[CrossRef](#)] [[PubMed](#)]
153. Wang, L.; Lankhorst, L.; Bernards, R. Exploiting Senescence for the Treatment of Cancer. *Nat. Rev. Cancer* **2022**, *22*, 340–355. [[CrossRef](#)]
154. Laberge, R.M.; Sun, Y.; Orjalo, A.V.; Patil, C.K.; Freund, A.; Zhou, L.; Curran, S.C.; Davalos, A.R.; Wilson-Edell, K.A.; Liu, S.; et al. MTOR Regulates the Pro-Tumorigenic Senescence-Associated Secretory Phenotype by Promoting IL1A Translation. *Nat. Cell Biol.* **2015**, *17*, 1049–1061. [[CrossRef](#)] [[PubMed](#)]
155. Herranz, N.; Gallage, S.; Mellone, M.; Wuestefeld, T.; Klotz, S.; Hanley, C.J.; Raguz, S.; Acosta, J.C.; Innes, A.J.; Banito, A.; et al. MTOR Regulates MAPKAPK2 Translation to Control the Senescence-Associated Secretory Phenotype. *Nat. Cell Biol.* **2015**, *17*, 1205–1217. [[CrossRef](#)] [[PubMed](#)]
156. Hu, Q.; Peng, J.; Jiang, L.; Li, W.; Su, Q.; Zhang, J.; Li, H.; Song, M.; Cheng, B.; Xia, J.; et al. Metformin as a Senostatic Drug Enhances the Anticancer Efficacy of CDK4/6 Inhibitor in Head and Neck Squamous Cell Carcinoma. *Cell Death Dis.* **2020**, *11*, 925. [[CrossRef](#)] [[PubMed](#)]
157. Fleury, H.; Malaquin, N.; Tu, V.; Gilbert, S.; Martinez, A.; Olivier, M.A.; Sauriol, A.; Communal, L.; Leclerc-Desaulniers, K.; Carmona, E.; et al. Exploiting Interconnected Synthetic Lethal Interactions between PARP Inhibition and Cancer Cell Reversible Senescence. *Nat. Commun.* **2019**, *10*, 2556. [[CrossRef](#)]
158. Wang, C.; Vegna, S.; Jin, H.; Benedict, B.; Lieftink, C.; Ramirez, C.; de Oliveira, R.L.; Morris, B.; Gadiot, J.; Wang, W.; et al. Inducing and Exploiting Vulnerabilities for the Treatment of Liver Cancer. *Nature* **2019**, *574*, 268–272. [[CrossRef](#)]
159. Prasanna, P.G.; Citrin, D.E.; Hildesheim, J.; Ahmed, M.M.; Venkatachalam, S.; Riscuta, G.; Xi, D.; Zheng, G.; van Deursen, J.; Goronzy, J.; et al. Therapy-Induced Senescence: Opportunities to Improve Anticancer Therapy. *J. Natl. Cancer Inst.* **2021**, *113*, 1285–1298. [[CrossRef](#)]
160. Amor, C.; Feucht, J.; Leibold, J.; Ho, Y.J.; Zhu, C.; Alonso-Curbelo, D.; Mansilla-Soto, J.; Boyer, J.A.; Li, X.; Giavridis, T.; et al. Senolytic CAR T Cells Reverse Senescence-Associated Pathologies. *Nature* **2020**, *583*, 127–132. [[CrossRef](#)]
161. Poblocka, M.; Basse, A.L.; Smith, V.M.; Falcicchio, M.; Manso, A.S.; Althubiti, M.; Sheng, X.; Kyle, A.; Barber, R.; Frigerio, M.; et al. Targeted Clearance of Senescent Cells Using an Antibody-Drug Conjugate against a Specific Membrane Marker. *Sci. Rep.* **2021**, *11*, 20358. [[CrossRef](#)] [[PubMed](#)]

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